

Amendments to the Specification

Please replace paragraph [0084] with the following paragraph:

EXAMPLE 3

Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Lidocaine Aerosol

[0084] A solution of 12.2 mg lidocaine in 100 μ L dichloromethane was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the lidocaine thin layer on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 5.0 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 2.4 microns with a geometric standard deviation of 2.1. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 g/cm³). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of 4.2×10^6 particles/mL. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time of 6 s, giving a rate of inhalable aerosol particle formation of 7.0×10^8 particles/second.

Table 1: Determination of the characteristics of a lidocaine condensation aerosol by cascade impaction using an Andersen 8-stage non-viable cascade impactor run at 1 cubic foot per minute air flow.

| Stage | Particle size range (microns) | Average particle size (microns) | Mass collected (mg) | Number of particles |
|-------|-------------------------------|---------------------------------|---------------------|---------------------|
| 0 | 9.0-10.0 | 9.5 | 0.1 | 2.2×10^5 |
| 1 | 5.8-9.0 | 7.4 | 0.3 | 1.4×10^6 |

| | | | | |
|---|---------|------|-----|-------------------|
| 2 | 4.7-5.8 | 5.25 | 0.1 | 1.3×10^6 |
| 3 | 3.3-4.7 | 4.0 | 0.7 | 2.1×10^7 |
| 4 | 2.1-3.3 | 2.7 | 0.9 | 8.7×10^7 |
| 5 | 1.1-2.1 | 1.6 | 1.0 | 4.7×10^8 |
| 6 | 0.7-1.1 | 0.9 | 0.5 | 1.3×10^9 |
| 7 | 0.4-0.7 | 0.55 | 0.2 | 2.3×10^9 |
| 8 | 0-0.4 | 0.2 | 0.0 | 0 |

Please replace paragraph [0085] with the following paragraph:

EXAMPLE 4

Drug Mass Density and Rate of Drug Aerosol Formation of Lidocaine Aerosol

[0085] A solution of 10.4 mg lidocaine in 100 μ L dichloromethane was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1g/cc, the calculated thickness of the lidocaine thin layer on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 4.2 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were sealed with parafilm, which was punctured with fifteen needles for air flow. The third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after 6 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with acetonitrile and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of lidocaine revealed that 3.1 mg of > 99% pure lidocaine had been collected in the flask, resulting in an aerosol drug mass density of 3.1 mg/L. The aluminum foil upon which the lidocaine had previously been coated was weighed following the experiment. Of the 10.4 mg originally coated on the aluminum, 10.2 mg of the material was found to have aerosolized in the 6 s time period, implying a rate of drug aerosol formation of 1.7 mg/s.

Please replace paragraph [0086] with the following paragraph:

EXAMPLE 5

Volatilization of Rizatriptan

[0086] A solution of 10 mg rizatriptan in 1 mL diethyl ether was spread out in a thin layer on a 10 cm x 15 cm sheet of aluminum foil. The diethyl ether was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the rizatriptan thin layer on the 150 cm² aluminum solid support, after solvent evaporation, is about 0.7 microns. The coated aluminum foil sheet was inserted into a glass tube in a furnace (tube furnace). A glass wool plug was placed in the tube adjacent to the foil sheet, and an air flow of 2 L/min was applied. The furnace was heated to 250 °C for 30 s to volatilize the coated rizatriptan and then was allowed to cool. The glass wool was extracted, and HPLC analysis of the collected material showed it to be at least 99% pure rizatriptan.

Please replace paragraph [0087] with the following paragraph:

EXAMPLE 6

Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Rizatriptan Aerosol

[0087] A solution of 11.3 mg rizatriptan in 200 µL dichloromethane was spread out in a thin layer on the central portion of a 4 cm x 9 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the rizatriptan thin layer on the 36 cm² aluminum solid support, after solvent evaporation, is about 3.1 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. One of the openings of the tube was sealed with a rubber stopper, another was loosely covered with the end of the halogen tube, and the third was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 7 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 1.2 microns with a geometric standard deviation of 1.7. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 g/cm³).

The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of 3×10^7 particles/mL. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time of 7 s, giving a rate of inhalable aerosol particle formation of 5×10^9 particles/second.

Table 1: Determination of the characteristics of a rizatriptan condensation aerosol by cascade impaction using an Andersen 8-stage non-viable cascade impactor run at 1 cubic foot per minute air flow.

| Stage | Particle size range (microns) | Average particle size (microns) | Mass collected (mg) | Number of particles |
|-------|-------------------------------|---------------------------------|---------------------|----------------------|
| 0 | 9.0-10.0 | 9.5 | 0.0 | 0 |
| 1 | 5.8-9.0 | 7.4 | 0.0 | 0 |
| 2 | 4.7-5.8 | 5.25 | 0.1 | 1.3×10^6 |
| 3 | 3.3-4.7 | 4.0 | 0.2 | 6.0×10^6 |
| 4 | 2.1-3.3 | 2.7 | 0.4 | 3.9×10^7 |
| 5 | 1.1-2.1 | 1.6 | 1.2 | 5.6×10^8 |
| 6 | 0.7-1.1 | 0.9 | 1.0 | 2.6×10^9 |
| 7 | 0.4-0.7 | 0.55 | 0.5 | 5.7×10^9 |
| 8 | 0-0.4 | 0.2 | 0.1 | 2.4×10^{10} |

Please replace paragraph [0088] with the following paragraph:

EXAMPLE 7

Drug Mass Density and Rate of Drug Aerosol Formation of Rizatriptan Aerosol

[0088] A solution of 11.6 mg rizatriptan in 200 μ L dichloromethane was spread out in a thin layer on the central portion of a 4 cm x 9 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the rizatriptan thin layer on the 36 cm² aluminum solid support, after solvent evaporation, is about 3.2 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. One of the openings of the tube was sealed with a rubber stopper, another was loosely covered with the end of the halogen tube, and the third was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after 7 s. The aerosol was allowed to sediment onto the walls of the 1 L flask

for approximately 30 minutes. The flask was then extracted with dichloromethane and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of rizatriptan revealed that 3.2 mg of > 99% pure rizatriptan had been collected in the flask, resulting in an aerosol drug mass density of 3.2 mg/L. The aluminum foil upon which the rizatriptan had previously been coated was weighed following the experiment. Of the 11.6 mg originally coated on the aluminum, all of the material was found to have aerosolized in the 7 s time period, implying a rate of drug aerosol formation of 1.7 mg/s.

Please replace paragraph [0090] with the following paragraph:

EXAMPLE 9

Vaporization of Zolmitriptan

[0090] A solution of 9.8 mg zolmitriptan in 300 μ L dichloromethane was spread out in a thin layer on a 4 cm x 9 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1g/cc, the calculated thickness of the zolmitriptan thin layer on the 36 cm² aluminum solid support, after solvent evaporation, is about 2.7 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a glass tube sealed at one end with a rubber stopper. Subjecting the bulb to one 15s, 60 v (variac) treatment afforded volatilized zolmitriptan on the glass tube walls. HPLC analysis of the collected material showed it to be at least 98% pure zolmitriptan. To obtain higher purity aerosols, one can coat a lesser amount of drug, yielding a thinner film to heat. A linear decrease in film thickness is associated with a linear decrease in impurities.

Please replace paragraph [0091] with the following paragraph:

EXAMPLE 10

Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Zolmitriptan Aerosol

[0091] A solution of 3.2 mg zolmitriptan in 100 μ L methanol was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1g/cc, the calculated thickness of the zolmitriptan thin layer on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 1.3 microns. The aluminum

foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were left open and the third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 6 s. The aerosol was analyzed by connecting the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 0.7 microns with a geometric standard deviation of 3.3. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 g/cm³). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of 4.9×10^7 particles/mL. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time of 6 s, giving a rate of inhalable aerosol particle formation of 8.1×10^9 particles/second.

Table 1: Determination of the characteristics of a zolmitriptan condensation aerosol by cascade impaction using an Andersen 8-stage non-viable cascade impactor run at 1 cubic foot per minute air flow.

| Stage | Particle size range (microns) | Average particle size (microns) | Mass collected (mg) | Number of particles |
|-------|-------------------------------|---------------------------------|---------------------|----------------------|
| 0 | 9.0-10.0 | 9.5 | 0.00 | 0 |
| 1 | 5.8-9.0 | 7.4 | 0.00 | 0 |
| 2 | 4.7-5.8 | 5.25 | 0.00 | 0 |
| 3 | 3.3-4.7 | 4.0 | 0.01 | 2.1×10^5 |
| 4 | 2.1-3.3 | 2.7 | 0.03 | 2.9×10^6 |
| 5 | 1.1-2.1 | 1.6 | 0.12 | 5.7×10^7 |
| 6 | 0.7-1.1 | 0.9 | 0.10 | 2.5×10^8 |
| 7 | 0.4-0.7 | 0.55 | 0.05 | 5.7×10^8 |
| 8 | 0-0.4 | 0.2 | 0.20 | 4.8×10^{10} |

Please replace paragraph [0092] with the following paragraph:

EXAMPLE 11

Drug Mass Density and Rate of Drug Aerosol Formation of Zolmitriptan Aerosol

[0092] A solution of 2.6 mg zolmitriptan in 100 μ L methanol was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The dichloromethane was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the zolmitriptan thin layer on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 1.1 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were left open and the third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after 6 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with acetonitrile and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of zolmitriptan revealed that 0.4 mg of > 96% pure zolmitriptan had been collected in the flask, resulting in an aerosol drug mass density of 0.4 mg/L. The aluminum foil upon which the zolmitriptan had previously been coated was weighed following the experiment. Of the 2.6 mg originally coated on the aluminum, 1.5 mg of the material was found to have aerosolized in the 6 s time period, implying a rate of drug aerosol formation of 0.3 mg/s.

Please replace paragraph [0099] with the following paragraph:

EXAMPLE 16

Particle Size, Particle Density, and Rate of Inhalable Particle Formation of Frovatriptan Aerosol

[0099] A solution of 5.0 mg frovatriptan in 100 μ L methanol was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The methanol was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the frovatriptan thin layer on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 2.0 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were left open and the third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within 1 s, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with collection of the aerosol terminated after 6 s. The aerosol was analyzed by connecting

the 1 L flask to an eight-stage Andersen non-viable cascade impactor. Results are shown in table 1. MMAD of the collected aerosol was 1.8 microns with a geometric standard deviation of 2.1. Also shown in table 1 is the number of particles collected on the various stages of the cascade impactor, given by the mass collected on the stage divided by the mass of a typical particle trapped on that stage. The mass of a single particle of diameter D is given by the volume of the particle, $\pi D^3/6$, multiplied by the density of the drug (taken to be 1 g/cm³). The inhalable aerosol particle density is the sum of the numbers of particles collected on impactor stages 3 to 8 divided by the collection volume of 1 L, giving an inhalable aerosol particle density of 7.3×10^5 particles/mL. The rate of inhalable aerosol particle formation is the sum of the numbers of particles collected on impactor stages 3 through 8 divided by the formation time of 6 s, giving a rate of inhalable aerosol particle formation of 1.2×10^8 particles/second.

Table 1: Determination of the characteristics of a frovatriptan condensation aerosol by cascade impaction using an Andersen 8-stage non-viable cascade impactor run at 1 cubic foot per minute air flow.

| Stage | Particle size range (microns) | Average particle size (microns) | Mass collected (mg) | Number of particles |
|-------|-------------------------------|---------------------------------|---------------------|---------------------|
| 0 | 9.0-10.0 | 9.5 | 0.01 | 1.3×10^4 |
| 1 | 5.8-9.0 | 7.4 | 0.02 | 8.0×10^4 |
| 2 | 4.7-5.8 | 5.25 | 0.03 | 3.8×10^5 |
| 3 | 3.3-4.7 | 4.0 | 0.05 | 1.6×10^6 |
| 4 | 2.1-3.3 | 2.7 | 0.09 | 9.1×10^6 |
| 5 | 1.1-2.1 | 1.6 | 0.16 | 7.6×10^7 |
| 6 | 0.7-1.1 | 0.9 | 0.09 | 2.4×10^8 |
| 7 | 0.4-0.7 | 0.55 | 0.04 | 4.0×10^8 |
| 8 | 0-0.4 | 0.2 | 0.0 | 0 |

Please replace paragraph [0100] with the following paragraph:

EXAMPLE 17

Drug Mass Density and Rate of Drug Aerosol Formation of Frovatriptan Aerosol

[0100] A solution of 5.0 mg frovatriptan in 100 μ L methanol was spread out in a thin layer on the central portion of a 3.5 cm x 7 cm sheet of aluminum foil. The methanol was allowed to evaporate. Assuming a drug density of about 1 g/cc, the calculated thickness of the frovatriptan thin layer on the 24.5 cm² aluminum solid support, after solvent evaporation, is about 2.0 microns. The aluminum foil was wrapped around a 300 watt halogen tube, which was inserted into a T-shaped glass tube. Both of the openings of the tube were left open and the third opening was connected to a 1 liter, 3-neck glass flask. The glass flask was further connected to a large piston capable of drawing 1.1 liters of air through the

flask. Alternating current was run through the halogen bulb by application of 90 V using a variac connected to 110 V line power. Within seconds, an aerosol appeared and was drawn into the 1 L flask by use of the piston, with formation of the aerosol terminated after 6 s. The aerosol was allowed to sediment onto the walls of the 1 L flask for approximately 30 minutes. The flask was then extracted with acetonitrile and the extract analyzed by HPLC with detection by light absorption at 225 nm. Comparison with standards containing known amounts of frovatriptan revealed that 0.85 mg of > 91% pure frovatriptan had been collected in the flask, resulting in an aerosol drug mass density of 0.85 mg/L. The aluminum foil upon which the frovatriptan had previously been coated was weighed following the experiment. Of the 5.0 mg originally coated on the aluminum, 2.8 mg of the material was found to have aerosolized in the 6 s time period, implying a rate of drug aerosol formation of 0.5 mg/s.